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STENT FOR BLOOD VESSEL AND MATERIAL FOR STENT FOR BLOOD
VESSEL

[Kekkan yoo stent oyobi kekkan yoo stent yoo sozai]

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1. Title of the invention

Stent for blood vessel and material for stent for blood vessel

Stent for blood vessel and material for stent for blood vessel

2. Technical field

The present invention relates to a stent for a blood vessel that can be inserted into a blood vessel, and more specifically, it relates to a stent for a blood vessel that supports a drug agent within the material that constitutes the stent.

3. Prior art

In angioplasty, there is a high likelihood that mechanical procedures such as balloon dilatation or stent implantation could cause damage to the blood vessels. In the sites in which the blood vessel has been damaged, there may sometimes be the occurrence of acute coronary occlusion resulting from thrombus formation, or of re-stenosis as brought about by proliferation of the intima of the blood vessel, which is a healing response by the vascular walls.

Thrombus formation is involved in the occurrence of acute coronary occlusion, and as means to prevent this, it is common to perform anti-thrombogenic treatment through the systemic administration of a drug agent via the veins.

On the other hand, re-stenosis can be brought about by excessive proliferation of cells. Currently, there is a great deal of research underway into drugs that can inhibit this type of cellular proliferation, and various types of drugs have shown good results.

However, in order to obtain the efficacy of these types of drug agents, it is necessary to perform systemic administration of a high concentration or a large amount of the drug agent, and there are indications of the risks of side effects resulting from this administration.

Therefore, in recent years, local drug delivery systems (LLDS) have been used as a safe and effective means to prevent acute coronary occlusion or re-stenosis. As one type of this LLDS, there have been various proposals for a method to place a catheter within the blood vessel, and to inject a drug agent into the targeted site, but in each of these proposals, it is necessary to maintain the catheter continuously within the blood vessel for a long period of time and to stop blood flow, which makes it difficult to obtain sufficient efficacy from the drug agent, and therefore, none of these proposals have yet reached practical application.

/4

Therefore, the item that is garnering the most attention now as an LLDS member to deliver a drug agent to the targeted blood vessel site is the stent. By supporting a drug agent in the stent, and then placing this stent into the targeted site, it is possible to perform localized administration of the drug agent. Also, the stent will not obstruct blood flow, and it can be maintained at the target site within the blood vessel for a long period of time, so it is possible to use this as an LLDS to obtain sufficient efficacy of the drug agent over a long period of time.

However, currently, all of the stents for blood vessels that are used clinically are made of metal.

Metal is a material in which it is not possible to mix a drug agent within the material itself, and the attachment of a drug agent can only be performed on the surface of the material. Examples of methods to attach a drug agent to a metal stent include methods such as coating, adhesion, or using a polymer sheet coating in which the drug agent has been mixed. When adding the drug agent to the surface of a metal stent using a coating method or an adhesion method, there may be problems in that the drug agent itself could

spall off of the stent surface. Also, it is difficult to attach enough drug agent in order to obtain sufficient drug effectiveness.

In methods to cover the metal stent using a polymer sheet, it is necessary to prepare the polymer sheet containing the drug agent under high temperature conditions, leading to concerns of a loss in the effectiveness of the drug agent.

In LDDS, it is necessary to control the content of the drug agent, the release amount per unit time, and the release time. In order to more effectively perform prevention of acute coronary occlusion or re-stenosis using LDDS, it is preferable to be able to perform control such that it is possible to maintain an effective concentration of the drug agent at the targeted blood vessel site, as well as to ensure that the drug agent is released into the blood vessel walls and into the blood over a specific period of time.

4. Disclosure of the invention

The present invention applies to the application of a stent that is composed of a biodegradable polymer material as an LDDS member, and aims to provide a stent for a blood vessel as well as the manufacturing method thereof in which it is possible to support a drug agent that can obtain sufficient drug efficacy with no loss of drug effectiveness onto the stent that is composed of a biodegradable polymer material, with no spalling of the drug agent off of the surface of the stent, in which it is possible to place the stent into the location of the targeted site within the blood vessel, and further, in which it is possible to ensure release of the effective concentration of the drug agent over the required period of time.

/5

In order to achieve the above aims, the present invention that is proposed herein is a stent that can be inserted within a blood vessel, in which this stent is formed in a tubular shape using a biodegradable polymer material, and in which the biodegradable polymer material that forms the stent is swollen to support a drug agent.

Also, the present invention is a stent for a blood vessel in which the biodegradable polymer material is swollen by keeping the biodegradable polymer material and the drug agent together for a specific period of time in a supercritical fluid, and in which the drug agent is supported on this swollen biodegradable polymer material.

Here, the drug agent to be supported on the biodegradable polymer material can be selected from amongst those materials that have thrombogenesis inhibition efficacy and/or intima proliferation inhibition efficacy.

The biodegradable polymer material that can be used here can be formed using an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

The present invention is a stent for a blood vessel in which, by further establishing a layer composed of a biodegradable polymer material onto the surface of the stent that is composed of a biodegradable polymer material that was swollen to support a drug agent, it is possible to control the release rate of the drug agent that has been supported on the biodegradable polymer material that forms this stent.

Also, the present invention is a stent for a blood vessel in which there is a laminated formation of biodegradable polymer layers containing a drug agent in which one or more coatings of a biodegradable polymer material containing a drug agent have been applied to the surface of a stent that is composed of a biodegradable polymer material that was swollen to support a drug agent.

The afore-mentioned biodegradable polymer layers that are formed on the surface of the stent can be formed of an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

A drug agent can be contained within the biodegradable polymer layer that is applied as a coating onto the surface of the stent. Here, the drug agent that can be used can be selected from amongst those drugs that have thrombogenesis inhibition activity.

Also, it is acceptable to laminate multiple layers of a biodegradable polymer layer containing a drug agent and a biodegradable polymer layer, at least one by one, onto the surface of the stent.

Further, it is acceptable for the multiple biodegradable polymer layers that are formed on the surface of the stent to contain drug agents with different drug effectiveness.

/6

The present invention is a stent for a blood vessel in which a sufficient amount of drug agent has been supported onto the biodegradable polymer material as a result of the swelling of this material.

The stent for a blood vessel according to the present invention is a material in which it is possible to support a sufficient amount of drug agent, with no losses of drug effectiveness or spalling, making it possible to ensure release of the required amount of drug agent into the blood vessel walls and blood over the required period of time.

Also, the stent for a blood vessel according to the present invention is a material in which release of the drug agent that has been supported within the stent is performed accompanying decomposition of the biodegradable polymer material that constitutes the stent, so it is possible to accurately release the drug agent into the targeted site within the blood vessel in which the stent has been installed.

By forming a further biodegradable polymer layer on the surface of the stent, it is possible to control the release rate of the drug agent as supported within the stent into the blood.

By including the drug agent within the biodegradable polymer layer that was further formed on the surface of the stent, it is possible to ensure release of multiple drug agents at different times within the blood vessel. For instance, by including a drug agent that has thrombogenesis inhibition efficacy within the biodegradable polymer layer, and by supporting a drug agent with intima proliferation inhibition activity within the biodegradable polymer material that constitutes the stent, it is possible to ensure release of the drug agent having the thrombogenesis inhibition activity into the blood vessel first, followed by the release of the drug agent having the intima proliferation inhibition activity.

The support of the drug agent in the stent can be performed by swelling the biodegradable polymer material prior to the formation of the stent, and then forming the stent. Similarly, it is acceptable to form the biodegradable polymer layer containing the drug agent or the biodegradable polymer layer onto the surface of the biodegradable polymer material prior to the formation of the stent, and then to form the stent using the biodegradable polymer material on which this biodegradable polymer layer was formed.

Other aims of the present invention as well as the specific benefits to be obtained as a result of the present invention will become clearer from the examples of embodiment that will be explained below.

5. Brief explanation of the drawings

Figure 1 is an angled view showing one example of the stent for a blood vessel according to the present invention.

Figure 2 is an angled view showing another example of the stent for a blood vessel according to the present invention.

Figure 3 is an angled diagram showing yet another example of the stent for a blood vessel according to the present invention.

Figure 4 is an angled diagram showing yet another example of the stent for a blood vessel according to the present invention.

Figure 5 is a block diagram showing the apparatus that can be used in order to support the drug agent onto the stent for a blood vessel according to the present invention.

Figure 6 is a cross-sectional diagram showing the fibers that form the biodegradable polymer layer containing the drug agent on the surface of the biodegradable polymer fibers that constitute the stent for a blood vessel according to the present invention.

Figure 7 is a cross-sectional diagram showing the fibers that form the biodegradable polymer layer on the surface of the biodegradable polymer fibers that constitute the stent for a blood vessel according to the present invention.

Figure 8 is a diagram showing the relationship between the pressure of the CO₂ supercritical fluid and the tensile strength of the PLLA fibers.

Figure 9 is a diagram showing the relationship between the temperature of the CO₂ supercritical fluid and the tensile strength of the PLLA fibers.

Figure 10 is a diagram showing the relationship between the pressure of the CO₂ supercritical fluid and the amount of drug agent that can be supported on the stent.

Figure 11 is a diagram showing the relationship between the temperature of the CO₂ supercritical fluid and the amount of drug agent that can be supported on the stent.

Figure 12 is a properties diagram showing the release behavior of the tranilast that has been supported on the stent according to the present invention.

Figure 13 is a properties diagram showing the release behavior of the tranilast that has been supported on the stent on which a biodegradable polymer film was formed.

Figure 14 is a properties diagram showing the release behavior of the tranilast that has been supported on the stent on which a biodegradable polymer film containing the drug agent heparin was formed.

6. Best embodiments of the invention

Below, we will explain the stent for a blood vessel and the manufacturing method therein according to the present invention in more detail while referring to the drawings.

The stent for a blood vessel according to the present invention is a material in which a biodegradable polymer

material such as biodegradable polymer fibers or a biodegradable polymer sheet is formed in a tubular shape such that it can be placed in a specific site within a blood vessel, and in which the biodegradable polymer material that constitutes the stent is swollen, and a drug agent that has, for instance, thrombogenesis inhibition efficacy or intima proliferation inhibition efficacy is supported on this swollen biodegradable polymer material. /8

The stent for a blood vessel 1 according to the present invention can be formed in a tubular shape, a columnar shape, or in particular, a cylindrical shape by wrapping the biodegradable polymer fibers 2 in a helical shape while bending the material in a zigzag fashion such that a continuous V-shape is formed, as shown in Figure 1.

Also, as another example of the stent for a blood vessel 1, as shown in Figure 2, the material in which the biodegradable polymer fibers 2 have been formed in a tubular shape, a columnar shape, or in particular, a cylindrical shape in a non-woven, non-knitted state can be used. A further example of the stent for a blood vessel 1 is a material in which a single biodegradable polymer fiber 2 has been knitted into a tubular shape as shown in Figure 3, and another examples is a material in which, as shown in Figure 4, a biodegradable polymer sheet unit 12 has been formed into a tubular shape, a columnar shape, or in particular, a cylindrical shape. The appropriate through-holes 13 can be opened in the sheet unit 12 in order to ensure that this stent 1 has flexibility.

These stents 1 are formed using the biodegradable polymer fibers 2 or the biodegradable polymer sheet unit 12, so after placement within the blood vessel of the subject, while the stent 1 will maintain its shape for a certain period of time, within approximately several months after placement in the blood vessel, it will decompose.

For this biodegradable polymer material, it is acceptable to use an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

More specifically, it is acceptable to use a material that is formed using one or more types of materials as selected from amongst poly-L-lactic acid (PLLA), polyglycolic acid, polyglactin, polydioxanone, polyglyconate, ϵ -caprolactone, a poly-lactic acid- ϵ -caprolactone copolymer, and a polyglycolic acid- ϵ -caprolactone copolymer.

For the biodegradable polymer material that constitutes the fibers or sheet unit, for instance, it is possible to use PLLA. PLLA can be manufactured by performing lactic acid fermentation of a natural shell material, and it is a material with superior biocompatibility. Therefore, a stent that is formed using

PLLA fibers or a PLLA sheet will have no adverse effects in relation to humans.

Also, when using a biodegradable polymer material as fibers, it is possible to use filaments. It is preferable that the filaments that are used are continuous monofilaments that will uniformly degrade within the body.

Also, for the drug agent to be supported on the swollen stent, it is possible to use drug agents that have thrombogenesis inhibition efficacy, such as heparin or ticlopidine, or to use drug agents that have intima proliferation inhibition efficacy, such as tranilast, pemirolast, or anti-cancer agents.

If the swelling temperature of the biodegradable polymer is higher than the thermal decomposition temperature of the drug agent, the drug agent could suffer thermal decomposition prior to being supported, resulting in a risk of a loss of drug effectiveness, so it is necessary to use a swelling temperature for the biodegradable polymer that is lower than the thermal decomposition temperature of the drug agent such that there will be no loss of the drug effectiveness of the drug agent.

By maintaining the stent that is formed using the afore-mentioned biodegradable polymer material and the drug agent within a supercritical fluid for a specific period of time, the stent will swell, and by supporting the drug agent on this swollen stent, it is possible to obtain the stent for a blood vessel according to the present invention.

When the drug agent to be supported is not easily dissolved within the supercritical fluid, it is possible to increase the support amount of the drug agent by adding a solvent such as water or ethanol.

Below, we will explain the specific methods to swell the stent that is formed using the biodegradable polymer

material using a supercritical fluid, and to support a drug agent on this swollen stent.

Here, we will explain an example in which CO₂ is used as the supercritical fluid, but it is acceptable to use a substance other than CO₂ as long as it is a substance that is compatible with humans, and for instance, it is acceptable to use H₂O.

In order to swell the stent using a supercritical fluid, and in order to support a drug agent on this swollen stent, it is possible to use the apparatus 21 that is constructed as shown in Figure 5. This apparatus 21 is comprised of a CO₂ cylinder 22, a compressor 23 to pressurize the CO₂, a heater 24 to heat the CO₂, and the reaction chamber 27 to react the CO₂ in a supercritical state, the stent 1, and the drug agent 26.

First, any of the stents 1 and drug agents 26 described above are placed into the reaction chamber 27. At this time, the stent 1 and the drug agent 26 are separated by the porous filter 28 in order to prevent mixing. /10

Next, the first valve 29 is opened to discharge the CO₂ from the CO₂ cylinder 22, and the discharged CO₂ is pressurized by the compressor 23. Then, the second valve 30 is opened, and the pressurized CO₂ is injected into the reaction chamber 27. At this time, the injected CO₂ must be set to a pressure that is equal to or greater than the CO₂ critical pressure and that is also equal to or less than the pressure at which the stent 1 will degrade. Also, it is even more preferable for the pressure of the injected CO₂ to be equal to or less than the pressure at which it is possible to maintain the tensile strength of the fibers when the stent 1 has been formed using biodegradable polymer fibers.

The critical pressure of the CO₂ which is used in this example as the supercritical fluid is 7.38 MPa. Therefore, the pressure within the reaction chamber 27 must be 7.38 MPa or more. Further, according to experiments performed by

the present inventors, when the stent 1 is formed of biodegradable polymer fibers, if the pressure within the reaction chamber 27 exceeds 24 MPa, the tensile strength of the biodegradable polymer fibers will degrade. In other words, it is necessary to ensure that the pressure within the reaction chamber 27 is 24 MPa or less.

At this time, the temperature within the reaction chamber 27 into which the CO₂ has been injected must be maintained, using the heater 24, at a temperature that is equal to or greater than the critical temperature of CO₂, but that is also equal to or less than the thermal decomposition temperatures of the biodegradable polymer and drug agent. Also, it is even more preferable that the temperature within the reaction chamber 27 into which the CO₂ was injected is set to a temperature that is equal to or less than the temperature at which the tensile strength of the biodegradable polymer fibers forming the stent 1 can be maintained.

The critical temperature of the CO₂ that is used as the supercritical fluid in this example is 31.3°C. The temperature within the reaction chamber 27 must be set to be 31.3°C or more. According to experiments performed by the present inventors, when the stent 1 is formed using PLLA fibers, if the temperature is higher than 140°C, the tensile strength of the PLLA fibers will degrade. Therefore, it is necessary to keep the temperature within the reaction chamber 27 to 140°C or less.

Because the CO₂ that was injected into the reaction chamber 27 is set to a pressure that is equal to or greater than its critical pressure, and a temperature that is equal to or greater than its critical temperature, it will become a supercritical fluid. Further, the supercritical fluid CO₂ will pass through the porous filter 28 together with the drug agent 26, and will be dispersed throughout the entirety of the reaction chamber 27. As a result, the stent

/11

1 will be immersed in the drug agent 26 and the supercritical fluid CO₂. By keeping the stent 1 for a specific period of time in this immersed state in the drug agent 26 and the supercritical fluid CO₂, the stent 1 will

swell, and the drug agent 26 will be supported on this swollen stent 1.

Finally, the third valve 31 is opened, and the CO₂ within the reaction chamber 27 is gradually discharged to bring the chamber to atmospheric pressure. As a result, the support of the drug agent 26 on the stent 1 will be completed, and it will be possible to obtain the stent for a blood vessel according to the present invention.

In the afore-mentioned method, the drug is supported onto the swollen stent after swelling the stent that has been formed using biodegradable polymer fibers, but it is also acceptable to swell the biodegradable polymer fibers prior to the formation of the stent, then to support the drug agent on these swollen biodegradable polymer fibers, and finally to form the biodegradable polymer fibers into a tubular shape, a columnar shape, or more particularly, a cylindrical shape.

The present invention is a material in which the properties of a supercritical fluid are employed, and a drug agent that has been dissolved by the supercritical fluid is supported as the polymer absorbs the solvent and swells, or in other words, the drug agent is supported through swelling of the biodegradable polymer material.

The stent for a blood vessel according to the present invention is formed using biodegradable polymer fibers, so after placement within the blood vessel of the subject, while it will maintain its shape for a certain period of time, it will degrade approximately several months after it has been placed in the blood vessel, and it will disappear within the biological tissue. The stent for a blood vessel according to the present invention is formed using a biodegradable polymer material that was swollen to support a drug agent, so the drug agent that has been supported on the biodegradable polymer material can be released into the blood vessel accompanying the decomposition of the biodegradable polymer material. Therefore, after the placement of the stent according to the present invention within the blood vessel, it is possible to continuously release the drug agent into the blood vessel accompanying

the decomposition of the biodegradable polymer material that constitutes the stent.

However, when it is necessary to strictly control the release of the drug agent that has been supported on the stent for a blood vessel into the blood vessel, for instance, in order to release a large amount of drug agent over a short period of time, it is possible to form a biodegradable polymer layer containing a drug agent on the surface of the stent by applying a coating of or adhering a biodegradable polymer containing a drug agent onto the surface of the stent. Also, in order to inhibit the release of a large amount of the drug agent in a short period of time from the stent that has been placed in the blood vessel, or in other words, to delay the release time of the drug agent that has been supported on the stent into the blood vessel, it is acceptable to form a further biodegradable polymer layer that is composed only of a

/12

biodegradable polymer onto the surface of the stent that is composed of a biodegradable polymer material that supports a drug agent.

The biodegradable polymer layer containing the drug agent or the biodegradable polymer layer can be formed by using a solvent such as acetone or the like, then by applying a coating of the solution containing a dissolved biodegradable polymer such as poly- ϵ -caprolactone onto the surface of the stent, or by immersing the stent within a solution containing the dissolved biodegradable polymer.

Further, the biodegradable polymer layer containing the drug agent and the biodegradable polymer layer can be formed in multiple layers on the surface of the stent. In this case, it is acceptable to intersperse the layers of the biodegradable polymer layer containing the drug agent and the biodegradable polymer layer, and further, to form multiple layers of biodegradable polymer layers containing drug agents with different drug efficacies.

The biodegradable polymer layer containing the drug agent and the biodegradable polymer layer can be formed not only on the surface of the stent, but can also be formed on

the surface of the biodegradable polymer material prior to the formation of the stent.

Next, we will provide a specific explanation of an example in which a further biodegradable polymer material layer has been formed on the surface of biodegradable polymer fibers that have been swollen to support a drug agent.

The biodegradable polymer fibers 14 that constitute the stent have been swollen to support the drug agent 17, as shown in Figure 6. On the surface of these fibers 14, there is a biodegradable polymer coating that contains the drug agent 16, and there is a biodegradable polymer layer 15 that contains a drug agent. As a result, the drug agent 16 that is contained within the biodegradable polymer layer 15 that has been formed on the surface of the fibers 14 will be released accompanying decomposition of the biodegradable polymer layer 15, and then, the drug agent 17 that was supported on the swollen biodegradable polymer fibers 14 will be released. The drug agent 16 that is attached to the surface of the fibers 14 can be the same drug agent as the drug agent 17 that is supported on the fibers 14, or these can be different drug agents. In other words, the drug agents to be released within the body using the stent for a blood vessel according to the present invention can be appropriately selected. Further, it is acceptable to establish multiple layers of the biodegradable polymer layer 15 that contains the drug agent. In this way, by establishing a biodegradable polymer layer 15 that contains a drug agent, it is possible to support a single or multiple drug agents on the stent, making it possible to perform further strict control of the drug

agent release time and drug agent release amount, or making it possible to release different drugs at the desired times. To put it another way, the thrombus formation that can contribute to acute coronary occlusion and the intima proliferation that can contribute to re-stenosis, where both of these occur within the blood vessels, can occur during a certain period of time after balloon dilatation surgery or stent implantation surgery. In other words, thrombus formation can occur immediately after surgery, and intima proliferation can occur within several weeks after surgery. In other words, as shown in Figure 6, by using a

/13

thrombogenesis inhibiting agent as drug agent 16 and by using an intima proliferation inhibiting agent as drug agent 17, it is possible to release the intima proliferation inhibiting agent over a long period of time after the thrombogenesis inhibiting agent has been quickly released, making it possible to prevent both acute coronary occlusion and re-stenosis using the same stent.

Also, in order to control the release rate of the drug agent that has been supported on the stent, as shown in Figure 7, it is possible to apply a further coating of a biodegradable polymer to form the biodegradable polymer layer 18 on the surface of the biodegradable polymer fibers 14 that support the drug agent 17 as a result of swelling and that form the stent. In this way, by forming the biodegradable polymer layer 18, after decomposition of the biodegradable polymer layer 18, the decomposition of the biodegradable polymer fibers 14 will begin, and the release of the supported drug agent 17 will be performed, making it possible to delay the release start time for the drug agent 17.

On the surface of the biodegradable polymer fibers 14, it is acceptable to form a multiple layer laminate of a biodegradable polymer layer 15 containing the drug agent 16 and a biodegradable polymer layer 18 that contains no drug agent. By using this type of structure, it is possible to perform strict control of the drug agent release time and the drug agent release amount, or to perform release of drug agents at different times as desired.

As described above, the stent for a blood vessel according to the present invention is a material in which the stent that is composed of a biodegradable polymer material is swollen, then a drug agent is supported on this swollen stent, and further, it is a material in which it is possible to support sufficient drug agent on the outer surface of the stent, with no issues of spalling of the drug agent off of the stent. Also, because the drug agent that has been supported on the stent will be released with the decomposition of the biodegradable polymer, it will be possible to control the release amount and release time of the drug agent.

7. Examples of embodiment

Below, we will explain the specific examples of embodiment of the present invention based on the test results.

<Experiment 1>

/14

In the present experiment, the pressure and temperature of the CO₂ were changed, multiple PLLA fibers supporting the drug agent were prepared, and measurements were made of the tensile strength of each of these PLLA fibers.

Example of embodiment 1

First, PLLA fibers with a diameter of 170 μ m and tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic acid), which has intima proliferation inhibition efficacy, were placed within the pressure vessel 27 of the apparatus 21 shown in Figure 5. At this time, a porous filter was placed between the PLLA fibers and the tranilast. Tranilast is a drug agent that has efficacy in inhibiting re-stenosis following angioplasty.

Next, CO₂ was pressurized to 10 MPa using the compressor 23, and by opening the second valve 30, it was injected into the pressure vessel 27. Then, the pressurized CO₂ within the pressure vessel 27 was heated up to 80°C, and was put in a supercritical fluid state.

Next, the PLLA fibers and the tranilast were kept within the supercritical fluid CO₂ for 2 hours, then gradually the CO₂ was discharged and the system was brought to atmospheric pressure. As a result, it was possible to obtain the PLLA fibers supporting the tranilast.

Examples of embodiment 2 - 13, Comparative example 1 and Comparative example 2

The same method as was used in Example of embodiment 1 was used to support tranilast on the PLLA fibers using the pressure and temperature conditions shown in the following Table 1.

Table 1

	Pressure (MPa)	Temperature (°C)	Tensile strength (N)
Example of embodiment 1	10	80	8
Example of embodiment 2	13	80	7.9
Example of embodiment 3	15	80	7.85
Example of embodiment 4	18	80	7.9
Example of embodiment 5	20	80	7.9
Example of embodiment 6	23	80	7.5
Example of embodiment 7	24	80	6.8
Example of embodiment 8	15	40	7.9
Example of embodiment 9	15	60	7.9
Example of embodiment 10	15	80	7.9
Example of embodiment 11	15	100	7.8
Example of embodiment 12	15	120	7.8
Example of embodiment 13	15	140	7.5
Comparative example 1	15	150	5
Comparative example 2	25	80	3

Comparative example 3

Other than placing no tranilast within the pressure vessel, the same method was used as was used in Example of embodiment 1 to immerse the PLLA fibers in the supercritical fluid CO₂.

Comparative examples 4 - 17

The same method was used as was used in Comparative example 3 to immerse the PLLA fibers within the supercritical fluid CO₂ under the pressure and temperature conditions shown in the following Table 2.

/16

Table 2

	Pressure (MPa)	Temperature (°C)	Tensile strength (N)
Comparative example 3	10	80	8.2
Comparative example 4	13	80	8.1
Comparative example 5	15	80	8.1
Comparative example 6	18	80	8.1
Comparative example 7	20	80	7.9
Comparative example 8	23	80	7.6
Comparative example 9	24	80	6.7
Comparative example 10	15	40	7.85
Comparative example 11	15	60	8
Comparative example 12	15	80	8.1
Comparative example 13	15	100	8
Comparative example 14	15	120	7.9
Comparative example 15	15	140	7.4
Comparative example 16	15	150	4.5
Comparative example 17	25	80	3

Tensile testing was performed on the PLLA fibers that were obtained in Examples of embodiment 1 through 13 and in Comparative examples 1 through 17 in order to investigate the tensile strength. The above Tables 1 and 2 and Figures 8 and 9 show the results of this testing.

As is clear in Figure 8 and Table 1, in Examples of embodiment 1 through 13, in which the CO₂ was made into a supercritical fluid at pressures of 10 - 24 MPa, the tensile strength of the PLLA fibers was 6.8 N or more, but in Comparative example 2, in which the CO₂ was made into a supercritical fluid at a pressure of 25 MPa, the tensile strength was 3 N. In other words, when supporting the tranilast on the PLLA fibers using CO₂ that was made into a supercritical fluid at a pressure higher than 24 MPa, the tensile strength will be reduced.

Figure 8 shows an example in which the PLLA fibers were immersed within the supercritical fluid CO₂ at 80°C for 2 hours at various pressures. /17

As is clear from Figure 9 and Table 1, in Examples of embodiment 1 through 13, in which the CO₂ was made into a supercritical fluid at temperatures ranging from 40 - 140°C, the tensile strength of the PLLA fibers was 6.8 N or more, but in Comparative example 1, in which the CO₂ was made into a supercritical fluid at a temperature of 150°C, the tensile strength was 5 N. In other words, when supporting the tranilast on the PLLA fibers using CO₂ that was made into a supercritical fluid at a temperature higher than 140°C, the tensile strength will be reduced. Therefore, it was determined that, by using a pressure of 7.38 - 24 MPa and a temperature of 31.3 - 140°C, it will be possible to maintain sufficient tensile strength in the PLLA fibers when supporting tranilast on PLLA fibers using CO₂ that was made into a supercritical fluid.

Figure 9 shows an example in which PLLA fibers were immersed within the CO₂ that was made into a supercritical fluid at a pressure of 15 MPa at various temperatures.

<Experiment 2>

In Experiment 2, the pressure and the temperature of the CO₂ were varied, and stents for blood vessels were formed using multiple biodegradable polymer materials supporting drug agents, and in particular, using biodegradable polymer fibers. Measurements were made of the

amount of drug agent supported on these stents for blood vessels.

Example of embodiment 14

As shown in Figure 1, a PLLA monofilament with a diameter of 170 μm was wound in a cylindrical shape by bending it in a zigzag fashion, resulting in a material that was used to form the cylindrical stent 1 with a diameter of approximately 3.5 mm and a length of approximately 12 mm.

This stent 1 and the tranilast were placed into the pressure vessel 27 of the apparatus 21 shown in Figure 5. At this time, a porous filter was placed between the PLLA monofilament and the tranilast.

Next, CO_2 was pressurized to 10 MPa using the compressor 23, and by opening the second valve 30, it was injected into the pressure vessel 27. Then, the pressurized CO_2 in the pressure vessel 27 was heated up to 80°C to change it into a supercritical fluid.

Examples of embodiment 15 - 25

The same method was used as was used in Example of embodiment 14, and the tranilast was supported on the stent under the pressure and temperature conditions shown in the following Table 3.

/18

The amount of tranilast supported on the stents that were obtained in Examples of embodiment 14 through 25 was measured using high-performance liquid chromatography. These results are shown in Table 3 and Figures 10 and 11.

Figure 10 shows an example in which the PLLA fibers were immersed for 2 hours within the supercritical fluid CO_2 at 80°C at various pressures.

Figure 11 shows an example in which the PLLA fibers were immersed within the supercritical fluid CO₂ at a pressure of 15 MPa at various temperatures.

Table 3

	Pressure (MPa)	Temperature (°C)	Tranilast support amount
Example of embodiment 14	10	80	50.2
Example of embodiment 15	13	80	55.3
Example of embodiment 16	15	80	56.1
Example of embodiment 17	18	80	59.3
Example of embodiment 18	20	80	60.7
Example of embodiment 19	24	80	61.5
Example of embodiment 20	15	40	30
Example of embodiment 21	15	60	35.4
Example of embodiment 22	15	80	56.6
Example of embodiment 23	15	100	57.2
Example of embodiment 24	15	120	60.3
Example of embodiment 25	15	140	62.0

As shown in Figures 10 and 11 and Table 3, by immersing the stent and tranilast within the supercritical fluid CO₂, it is possible to obtain the stent for a blood vessel according to the present invention on which the tranilast is supported. The supported tranilast is supported with no occurrence of thermal decomposition under these temperature conditions. This is because the critical temperature of CO₂ is low, and it is possible to support the tranilast on the stent without requiring immersion at a

/19
high temperature, so it is possible to use CO₂, with its low supercritical temperature, for a large number of drug agents.

Also, based on Examples of embodiment 14 through 25, it was determined that the support of tranilast onto the stent is dependent on the pressure and temperature of the supercritical CO₂, or in other words, that as the temperature used when forming CO₂ into a supercritical fluid is increased, the amount of drug that is supported will increase.

<Experiment 3>

In the present experiment, we investigated the drug agent release behavior of a stent on which a biodegradable polymer layer containing the drug agent poly-ε-caprolactone was formed on the surface of a stent formed using PLLA monofilaments, where this is a biodegradable polymer fiber supporting tranilast. This experiment was performed as an *in vitro* experiment. The drug agent release amount was measured using high-performance liquid chromatography.

Example of embodiment 26

The stent that was obtained in the afore-mentioned Example of embodiment 19 was immersed for 30 days within 1 ml of fetal bovine serum, and the release behavior of the tranilast that was released into the serum was investigated. Figure 12 shows the results of this study.

The stent that was used here was formed in a tubular shape with a diameter of approximately 3.5 mm and a length of approximately 12 mm.

Example of embodiment 27

A coating of poly-ε-caprolactone was applied at a thickness of approximately 10 μm onto the surface of the stent that was obtained in Example of embodiment 19, then the stent was immersed for 30 days within 1 ml of fetal bovine serum, and the drug agent release behavior of the tranilast that was released into the serum was investigated. Figure 13 shows the results of this study.

Example of embodiment 28

5 ml of heparin sodium (Shimizu Pharmaceuticals, containing 1,000 units of heparin as heparin sodium within 1 ml) that has thrombogenesis inhibition activity was mixed into a 40% solution in which poly- ϵ -caprolactone was dissolved in acetone, and the resultant solution was stirred to form a suspension. This suspension was applied as a coating onto the stent that was obtained in Example of embodiment 19, forming a coating of poly- ϵ -caprolactone containing 5% of heparin sodium on the surface of the stent at a thickness of approximately 10 μm . At this time, 12 μg (12×10^{-3} heparin units) of heparin sodium was contained within the poly- ϵ -caprolactone layer formed on the surface of the stent.

/20

This stent was immersed for 30 days within 1 ml of fetal bovine serum, and the drug agent release behavior of the tranilast and heparin sodium as released into the serum was investigated. Figure 14 shows the results of this study.

As is clear from Figure 12, after 14 days, approximately 65% of the tranilast that was supported on the fibers, in which the biodegradable polymer fibers forming the stent were swollen, was released, and the release continued thereafter, with 70% released after 30 days, making it clear that the drug release continued over a long period of time.

As is clear from Figure 13, the stent in which there was a coating of poly- ϵ -caprolactone at a thickness of approximately 10 μm on the surface of the stent showed no release of the tranilast that was supported on the biodegradable polymer fibers that constituted the stent up to 2 days after the start of the experiment, but after 2 days had elapsed, the same tranilast release behavior was seen as was seen with the stent that had no poly- ϵ -caprolactone coating. This is due to the fact that there was temporarily stoppage of release by the poly- ϵ -caprolactone that coated the surface of the stent, and so by applying a coating of a biodegradable polymer, it is possible to inhibit the release of the drug agent that is supported on the fibers constituting the stent until the desired time, and to start the release of the drug agent after a certain period of time has elapsed.

Further, as is clear in Figure 14, 66% of the heparin sodium that was applied as a coating onto the surface of the stent was released after 2 days, with 73% released after 7 days. On the other hand, no release of the tranilast was seen up to two days after the start of the experiment, but after 2 days had elapsed, the same release behavior was seen as was seen in the stent that had no poly- ϵ -caprolactone coating. Based on these results, it was determined that the heparin sodium that was contained within the poly- ϵ -caprolactone that coated the surface of the stent was immediately released into the serum, and the tranilast that was supported through swelling of the biodegradable polymer was gradually released.

The thrombus formation that can contribute to acute coronary occlusion and the intima proliferation that can contribute to re-stenosis, where both of these occur within the blood vessels, show a trend to occur within a certain period of time following balloon dilatation surgery or stent implantation surgery, with the thrombus formation occurring at an early stage after the surgery, and with the intima proliferation occurring over a long period of time after the surgery. Therefore, it is expected that the stent of the present experiment, in which heparin sodium, which has thrombogenesis inhibition activity, is released within a short period of time, and in which tranilast, which has intima proliferation inhibition activity, is released over a long period of time, could be an LDDS that could prevent both acute coronary occlusion and re-stenosis.

/21

8. Field of industrial application

As described above, the stent for a blood vessel according to the present invention is a material in which the stent that is composed of a biodegradable polymer material is swollen, and a drug agent is supported on this swollen stent, so it is possible to maintain a sufficient amount of the drug agent while preventing dislodging of the material from the stent, and it is possible to perform continuous release of the drug agent into the blood vessel over a long period of time.

Also, the present invention is a material in which a further biodegradable polymer layer is formed on the surface of the stent that is formed using a biodegradable polymer material or on the surface of a biodegradable polymer material supporting a drug agent and constituting the stent, so it is possible to control the release time of the drug agent supported on the stent into the body, making it possible to release the drug agent at the most preferable time.

Further, by forming a biodegradable polymer layer containing a further drug agent on the surface of the stent that is formed using a biodegradable polymer material or on the surface of the biodegradable polymer material, it is possible to perform release of multiple types of drug agents into the body at the appropriate times. Therefore, it is possible to control the drug agents to be released into the body, and to release multiple types of drug agents in the desired sequence.

/22

9. Scope of patent claims

1) A stent for a blood vessel to be introduced into a blood vessel, in which said stent is formed in a tubular shape using a biodegradable polymer material, and said biodegradable polymer material has been swollen to support a drug agent.

2) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that said biodegradable polymer material is a fiber material, and these fibers are knitted into a tubular or columnar shape.

3) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that said biodegradable polymer material is a fiber material, and these fibers are formed in a shape along the surface of a tubular or columnar form.

4) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 2 or Claim 3, that is characterized by the

fact that said biodegradable polymer fibers are a continuous filament.

5) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that said biodegradable polymer material is a sheet.

6) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that said biodegradable polymer material is an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

7) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that said drug agent has thrombogenesis inhibition efficacy and/or intima proliferation inhibition efficacy.

8) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that the swelling temperature of said biodegradable polymer material is lower than the thermal decomposition temperature of said drug agent.

9) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, that is characterized by the fact that, by keeping said biodegradable polymer material and said drug agent within a supercritical fluid for a specific period of time, it is possible to swell said biodegradable polymer material and to support the drug agent on said biodegradable polymer material.

10) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 9, which is characterized by the fact that said supercritical fluid has biocompatibility.

11) A manufacturing method for a stent for a blood vessel that is characterized by the fact that the stent that is

composed of said biodegradable polymer material will be swollen by a supercritical fluid within a pressure vessel /23
to support a drug agent on said biodegradable polymer material.

12) A manufacturing method for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 11, that is characterized by the fact that the pressure within said pressure vessel is equal to or greater than the critical pressure of said supercritical fluid and equal to or less than the pressure at which said biodegradable polymer material will degrade.

13) A manufacturing method for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 11, that is characterized by the fact that the temperature within said pressure vessel is equal to or greater than the critical temperature of said supercritical fluid and equal to or less than the thermal decomposition temperatures of said biodegradable polymer material and said drug agent.

14) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 1, which is characterized by the fact that there is a biodegradable polymer layer formed on the surface of said stent.

15) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 14, which is characterized by the fact that the biodegradable polymer layer that has been formed on the surface of said stent is formed using an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

16) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 14, which is characterized by the fact that a drug agent is contained within said biodegradable polymer layer.

17) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 14, which is characterized by the fact that a drug agent having thrombogenesis inhibition efficacy is contained within the biodegradable polymer layer formed as a coating on the surface of said stent.

18) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 14, which is characterized by the fact that at least one each of a biodegradable polymer layer containing a drug agent and a biodegradable polymer layer are laminated onto the surface of said stent.

19) A stent for a blood vessel as noted in Scope of Patent Claims, Claim 14, which is characterized by the fact that drug agents with different drug effectiveness are contained within the multiple biodegradable polymer layers that are formed on the surface of said stent.

20) A material for a stent to be used to form a stent for a blood vessel to be introduced into a blood vessel that is characterized by the fact that said material for a stent is a biodegradable polymer material, and not only is this material swollen to support a drug agent, there are biodegradable polymer layers formed as a laminate on the surface of this material.

/24

21) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that said biodegradable polymer material is an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

22) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that said biodegradable polymer material is a fiber.

23) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 22, which is characterized by

the fact that said biodegradable polymer fibers are a continuous filament.

24) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that said biodegradable polymer material is a sheet.

25) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, that is characterized by the fact that the biodegradable polymer that is laminated onto the surface of said biodegradable polymer material is an aliphatic polyester, an anhydrous aliphatic acid, an aliphatic polycarbonate, polyphosphazene, or a copolymer containing at least one of these.

26) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that the drug agent to be supported on said biodegradable polymer material has thrombogenesis inhibition efficacy and/or intima proliferation inhibition efficacy.

27) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that a drug agent is contained in said biodegradable polymer layer.

28) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 27, that is characterized by the fact that said drug agent is a drug agent with thrombogenesis inhibition efficacy.

29) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that at least one each of a biodegradable polymer layer containing a drug agent and a biodegradable polymer layer are laminated onto the surface of said material for a stent.

30) A material for a stent for a blood vessel as noted in Scope of Patent Claims, Claim 20, which is characterized by the fact that drug agents with different drug effectiveness are contained within the multiple biodegradable polymer layers that are formed on the surface of said material for a stent.

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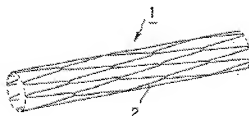


Figure 1

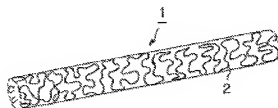


Figure 2

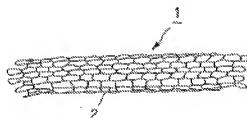


Figure 3

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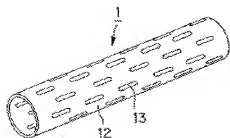


Figure 4

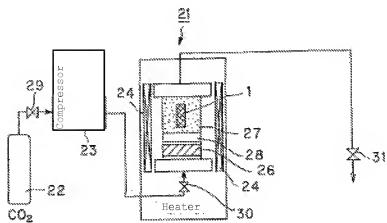


Figure 5

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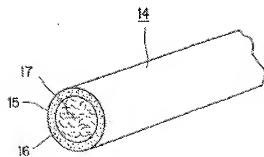


Figure 6

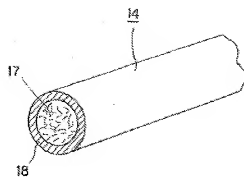


Figure 7

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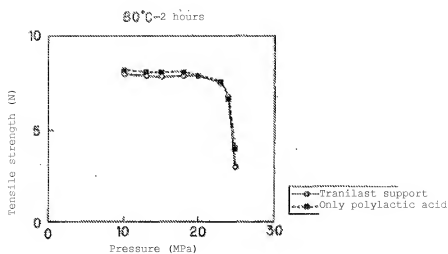


Figure 8

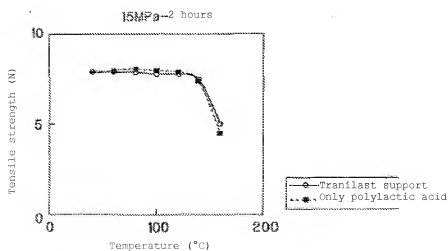


Figure 9

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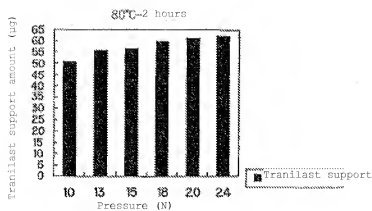


Figure 10

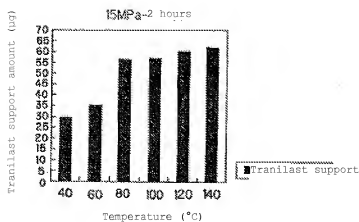


Figure 11

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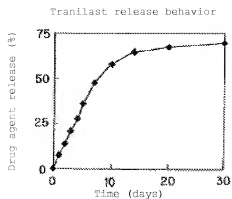


Figure 12

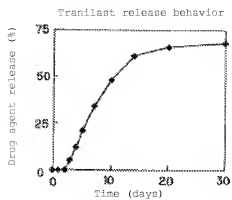


Figure 13

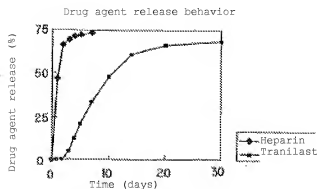


Figure 14